REMARKS

In the Office Action, the Examiner indicated that claims 1 through 28 are pending in the application, claims 9 to 14 and 16 to 28 have been withdrawn, and that claims 1 to 8 and 15 have been rejected.

Applicants have amended claims 1 to 3, 5, 7, 8, and 15. Claim 4 has been canceled without prejudice. Claims 29 to 30 have been added. Accordingly, claims 1 to 3, 5 to 9, 15, and 29 to 30 are presented for examination.

Each of the Examiner's objection and rejections is discussed below in the order in which they were presented. Applicants respectfully request that prior to reviewing this reply in detail that the Examiner contact the undersigned to discuss an interview.

The Claim Objections

On page 2 of the Office Action, the Examiner objected to claims 1 to 8 and 15 because the claims have not been amended to reflect the election made in the response to the restriction requirement. Applicants have amended claims 1 to 8 and 15 in accordance with the Examiner's requirement.

In addition, the Examiner objected to claims 5 to 8 for being of improper dependent form. Applicants have re-written claim 5 as an independent claim in accordance with the Examiner's requirement.

Claim Rejections, 35 U.S.C. §112, second paragraph

On pages 3-4 of the Office Action, the Examiner rejected claims 7 and 8 under 35 U.S.C. §112, second paragraph. Claim 7 has been amended to depend from claim 5. Claim 8 has been amended to recite an "epitopic peptide" instead of an "oligopeptide. Applicants submit that this overcomes the rejections under 35 U.S.C. §112, second paragraph. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims under 35 U.S.C. §112, second paragraph.

Claim Rejections, 35 U.S.C. §112, first paragraph (written description)

On page 5-7 of the Office Action, the Examiner rejected claims 1 to 8, and 15 under 35 U.S.C. §112, first paragraph (written description). In particular, the Examiner has asserted that due to the use of the open transitional phrase "comprising", there is substantial variability among the species encompassed within the scope of the claims.

Applicants respectfully traverse the rejection.

35 U.S.C. §112, first paragraph recites, "The specification shall contain a written description of the invention...". Claim 1, and those claims dependent thereon, is directed to an oligopeptide or peptide comprising SEQ ID NO: 4. In other words, the presently claimed invention is directed to amino acid sequences, of 8 to about 30 amino acids in length, comprising SEQ ID NO: 4, which is 9 amino acids in length.

Accordingly, the oligopeptide or peptide of claim 1 must comprise the novel sequence of SEQ ID NO: 4. In theory, SEQ ID NO: 4 could be coupled or associated with any other molecule.

In claim 1 SEQ ID NO: 4 is covalently linked to 0 to about 21 amino acids, that is, the 9 amino acids of SEQ ID NO: 4 and up to about 21 other amino acids, resulting in an oligopeptide of about 30 amino acids. The identity of these 0 to about 21 amino acids is not relevant to the patentability of an oligopeptide or peptide comprising SEQ ID NO: 4. Applicants submit that the use of the term "comprising" allows additional elements to be added to the claimed invention, but that these elements are not essential to patentability. MPEP §2111.03 recites:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., >Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps.");< Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

As noted above, "comprising" leaves the claim open for the inclusion of unspecified ingredients even in major amounts. Accordingly, the additional amino acid sequences need not be specified.

Accordingly, the Examiner's written description rejection amounts to the suggestion that applicants have not demonstrated possession of amino acid sequences unrelated to patentability and which have not been assigned a function. In addition, the MPEP states that the additional amino acid sequences need not be specified. Thus, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. §112, first paragraph (written description).

In addition, the Examiner has asserted that claims 2 to 4 have been rejected under 35 U.S.C. §112, first paragraph (written description). Claim 4 has been canceled without prejudice. Claims 2 and 3 are directed to oligopeptides comprising, respectively, at least two and at least three epitopic peptide sequences. The Examiner has asserted that the specification does not clearly allow a person of ordinary skill in the art to recognize that applicants were in possession of an oligopeptide comprising at least two or at least three epitopic peptide sequences.

Applicants respectfully traverse the rejection.

Applicants have disclosed 20 different epitopic peptide sequences (SEQ ID NOS: 1-20). In addition, paragraph [0048] of the application recites, "The present invention is also directed to an isolated polypeptide, especially one having immunogenic activity, the sequence of which comprises within it one or more stretches comprising any 2 or more of the sequences of SEQ ID NO: 1-20 and in any relative quantities...". As the sequences of SEQ ID NOS: 1 to 20 are known, the complete structure of oligopeptides comprising at least two or at least three epitopic peptide sequences is easily ascertained. As the structure of the oligopeptides of claims 2 and 3 is known, the skilled artisan would recognize that applicants were in possession of the invention defined by claims 2 and 3. Thus, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims 2 and 3 under 35 U.S.C. §112, first paragraph (written description).

Claim Rejections, 35 U.S.C. §112, first paragraph (enablement)

On page 7-11 of the Office Action, the Examiner rejected claim 15 under 35 U.S.C. §112, first paragraph (enablement). Applicants respectfully traverse this rejection.

Claim 15 is directed to vaccine compositions comprising the oligopeptides or peptides of the present invention, including the oligopeptide or peptide of claim 1, wherein animal subjects treated with the oligopeptide or peptide produce antibodies or cells that react with the oligopeptide or peptide upon administration of the oligopeptide or peptide to the subject.

Applicants submit that the proper standard for a §112, first paragraph, enablement rejection is whether the application contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. MPEP §2164.01. Accordingly, the issue is whether one of skill in the art having the present specification before him could make and use the claimed invention without undue experimentation.

In the discussion which follows, applicants present why undue experimentation is not required given the knowledge in the art and the guidance provided by the specification.

Claim 15, Directed to Vaccines, is Enabled

The examiner stated that the specification fails to teach how to use the claimed immunogens as a vaccine for treatment of cancer without undue experimentation. As discussed below, the present application clearly teaches how to prepare a vaccine to provoke the subject's immune response against cancerous cells. Claim 15, as presently amended, recites:

> 15. A vaccine composition comprising an oligopeptide or peptide of claim 1, 2, 3, 5, 6, 7, 8, or 9 present in a pharmaceutically acceptable carrier and in an amount sufficient to elicit production of antibodies or cells that react with said oligopeptide or peptide when said oligopeptide or peptide is administered to an immunologically competent animal.

As the Examiner knows, a vaccine is a composition that utilizes an antigen to provoke an immune response against a target bearing the antigen. The vaccine of claim 15 includes an antigen in the form of an oligopeptide or peptide. Paragraph [0025] of the application recites, "The antigen is considered immunogenic if it is capable of inducing a CTL-mediated immune response". The issue is whether one of skill in the art, having the present specification, could determine if antibody-based or cellular immunity has been produced following vaccination. Assays to determine if there is an antibody or cell-based immune reaction to an oligopeptide or peptide are well known in the art (Slingluff, C.L. et al. Clinical and Immunologic Results of a Randomized Phase II Trial of Vaccination Using Four Melanoma Peptides Either Administered in Granulocyte-Macrophage Colony-Stimulating Factor in Adjuvant or Pulsed on Dendritic Cells. 2003 *J. Clin. Oncology* 21(21):4016-4026; Pavlenko M. et al. A phase I trial of DNA vaccination with a plasmid expressing prostate-specific antigen in patients with hormone-refractory prostate cancer. 2004 *British J. Cancer* 91:688-694; and Dols, A. et al. Identification of Tumor-Specific Antibodies in Patients With Breast Cancer Vaccinated With Gene-Modified Allogeneic Tumor Cells. 2003 *J. Immunotherapy* 26(2):163-170; copies enclosed).

Antibodies or cells that react with the oligopeptides or peptides results in treatment of a disease, in this case, cancer. The examiner has acknowledged that claim 15 is enabled with regard to antibody production. Given that techniques are well-known in the art to assay for the presence of such antibodies and their reactivity with target cells, applicants submit that undue experimentation is not necessary. Undue experimentation is not based on the quantity of experimentation. MPEP §2164.06 recites:

> "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Given that techniques are well-known in the art to assay for the presence of such antibodies and their reactivity with target cells, applicants submit that the present specification has provided a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Thus, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claim 15 under 35 U.S.C. §112, first paragraph (enablement).

Although claim 15 makes no recitation of "treatment of cancer", applicants have addressed the Examiner's assertions in regard to vaccines for treatment of cancer below.

An Explanation of Immune Tolerance

Given the Examiner's comments on pages 8 to 11 of the present Office Action, applicants believe it would be helpful to provide a discussion of tolerance in the context of the present invention. The examiner is correct in stating that cytotoxic T lymphocyte (CTL) tolerance must be overcome to effectively stimulate an immune response against tumor cells. Immunotherapy as practiced in the present invention breaks tolerance by activating a CTL response against immunogenic antigens through presentation and activation by Antigen Presenting Cells (APCs). The

invention teaches a method for selecting the right antigens, which, when presented in the right way by vaccination, will effectively break tolerance and lead to tumor rejection.

Tolerance occurs when CTL do not recognize tumor-associated self antigens (for example, mutations arising in oncogenesis or proteins over-produced by tumor cells), and the tumor is able to exist and proliferate in the body undetected by the immune system. As embodied in the present invention, effective use of certain MHC-associated, tumor-associated antigenic epitopes in an immunotherapy setting can break tolerance and enable CTL to recognize and destroy the tumor cells that display these tumor expressed tumor-associated antigen (TAA) in the context of MHC molecules.

Even if T cells have been tolerized to one or more of these self peptides prior to vaccination, the tolerance can be broken by APC-mediated activation of new T cell clones *in vivo* by vaccination using methods well known in the art at the time the invention was made (recent publications include: Gross et al, Okano et al., den Boer et al), or *in vitro* as described in detail in the specification (paragraphs [0101-0107]).

Immunotherapeutic vaccination as disclosed in the present invention presents synthetic versions of antigens which are injected into the patient as oligopeptides/peptides or as nucleic acids in a vector. The peptides are processed through the MHC pathway and displayed on the APC surface to activate T cells. Once the CTL are activated by APC, they can circulate throughout the body to seek out, recognize and destroy tumor cells that display similar MHC-associated antigens.

Even if T cells have been tolerized to one or more of these self peptides prior to vaccination, the tolerance can be broken by APC-mediated activation of T cell clones using methods well known in the art (for example, den Boer et al. 2001 167:2522-28).

The immunogenic peptides disclosed in the application may be used not only for therapeutic purposes, but CTL recognition (breaking of tolerance) may be used to screen patient samples (e.g., tumor, peripheral blood) for the presence of CTLs that specifically recognize the epitopes. The results of screening also help determine efficacy of proceeding with a regimen of treatment using the antigens disclosed in the application. If CTL from patient samples are able to recognize epitopes *in vitro*, this is an indication that tolerance has been broken, and that the patients are likely to respond *in vivo*, as long as CTL are activated through *in vivo* presentation of the peptides by APC. Ramakrishna et al. (International Immunology 15(6):751-63, 2003; copy enclosed) demonstrated that when the peptides of SEQ ID NO:1-16 were pulsed onto dendritic cells (a type of APC), CTL were generated *in vitro* against all of these synthetic peptides. These peptide-specific CTL were able to lyse freshly isolated cells from primary ovarian tumors and ovarian tumor cell lines, but were not reactive toward normal ovary tissue. These data demonstrate that: 1) the peptides of SEQ ID NO: 1-16 were able to elicit a CTL response against tumor cells, 2) tolerance to these peptides was broken using APC to activate naive T cells, which is the same principle applied in immunotherapeutic vaccination.

Predictability

The Examiner states several times that the current state of the art teaches that cancer therapy using a vaccine comprising a polypeptide is unpredictable, and that the specification fails to teach now administration of the claimed polypeptide addresses this unpredictability.

Applicants submit that there was ample evidence in the art at the time the invention was made that human tumor-reactive CTL can control a number of types of cancer in humans and rodent models. What the art did not teach was how to identify peptides that would stimulate T cells for an effective tumor rejection response. The specification points out the other methods typically used for antigen identification, such as motif analysis and genetic screening, which would yield unpredictable results if they do not additionally take into account whether or not the peptide antigens derived by these methods are also present on the tumor surface and associated with MHC Class I molecules. The paper by Ramakrishna (copy enclosed) confirms that all of the 16 peptides tested and also disclosed in this invention stimulated a CTL response against primary and established tumor cells, indicating the highly predictable nature of this approach (16 out of 16 successful).

Discussion of Art Cited

Applicants believe the publications relied on by the Examiner in presenting the §112, first paragraph, (enablement) rejection do not support the Examiner's position because these publications are not relevant or actually support rather than undermine applicants assertion of enablement. Each of the publications cited by the Examiner in the enablement rejections are discussed below.

Lauritzsen et al.

The paper by Lauritzsen et al. is not relevant to the present invention as it discusses CD4+ T cells that recognize antigens that bind MHC Class II antigens and help mediate antibody responses. The present invention is directed to CD8+ T cell-mediated CTL responses toward MHC Class I-associated antigens. These two types of T cells act through different mechanisms.

Sarma et al.

The paper by Sarma et al. supports the concepts disclosed in the invention. In this study, P1A antigen, a prototypical unmutated tumor antigen, was expressed at low levels on normal mouse cells, including lymphoid tissues. Transgenic expression of the P1A antigen in the thymus induced T cell clonal deletion, indicating that the P1A antigen was processed and presented, and that P1A –specific T cells were susceptible to clonal deletion. However, when the transgenic mice were challenged with tumor cells that displayed both the P1A antigen and the Costimulatory Signal B7+, these tumors were recognized by CTL and rejected. Tumor cells displaying P1A but lacking B7 were not recognized, thus demonstrating that the combination of antigen and costimulatory signal displayed on the same cell breaks tolerance and activates T cells against a prototypical, unmutated tumor-associated self antigen, the same principle applied in immunotherapeutic vaccination and disclosed in the invention.

Sherman et al.

Sherman et al. studied T cell immunotherapy and self-tolerance to several predicted motif epitopes of p53 of varying avidity. In this study, the authors use a transgenic HLA A2.1 mouse model to determine which of several epitopes were able to lyse human cells expressing p53 and the

A2.1 allele. The study suggests that high avidity epitopes are more readily eliminated, and that the degree of self-tolerance varies depending upon avidity. The authors suggest that a residual, low avidity repertoire of epitopes remains available to respond to a p53 vaccine. The antigens of the present invention are lower rather than very high avidity epitopes, suggesting that the tendency toward self-tolerance would be lower and the possibility for activation through APC presentation would be even more likely for lower avidity epitopes such as those disclosed in the invention.

Each of the papers by Sarma et al. and Sherman et al. describe epitopes generated by motif analysis and not naturally processed antigens isolated from tumor cells.

Motif art teaches away from using low avidity epitopes such as those described in the invention. Indeed, studies performed subsequent to Sherman and the filing of this application supports the assertion that lower avidity epitopes, if presented on the tumor surface, may be better choices for effective vaccination leading to tumor rejection (Gross et al J. Clin Invest 2004 113:425-33; Okano et al J. Immunol 2005 174:2645-52).

Claim Rejections, 35 U.S.C. §102(b)

On pages 11-12 of the Office Action, the Examiner rejected claims 1 and 15 under 35 U.S.C. §102(b) as being anticipated by Adachi et al. (*Nucleic Acids Research*, vol. 20, pp. 5297-5303 (1992)) ("Adachi"), and on page 12 of the Office Action, the Examiner rejected claims 5, 7 and 8 under 35 U.S.C. §102(b) as being anticipated by SEQ ID NO: 30 of U.S. Patent No. 5,645,994 to Huang ("Huang"). The MPEP and case law provide the following definition of anticipation for the purposes of 35 U.S.C. §102:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP §2131 citing *Verdegaal Bros. v. Union Oil Company of California*, 814 F.2d 628, 631, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987).

Applicants have amended claims 1 and 5 to recite "an isolated oligopeptide or peptide". The terms "oligopeptide" and "peptide" are defined in paragraphs [0022] and [0023] of the application, respectively, which recite:

> [0022] The term "peptide" is used herein to designate a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The peptides are typically 9 amino acids in length, but can be as short as 8 amino acids in length, and as long as 14 amino acids in length.
>
> [0023] The term "oligopeptide" is used herein to designate a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The length of the oligopeptide is not critical to the invention as long as the correct epitope or epitopes are maintained therein. The oligopeptides are typically less than about 30 amino acid residues in length, and greater than about 14 amino acids in length.

Accordingly, oligopeptides are about 14 to about 30 amino acids in length, and peptides are 8 to 14 amino acids in length. Thus, presently amended claims 1 and 5 comprise amino acid sequences of 8 to about 30 amino acids in length.

The polypeptides disclosed by Adachi are over 1400 amino acids in length. SEQ ID NO: 30 of Huang is 142 amino acids in length. Accordingly, Adachi and Huang do not anticipate presently amended claims 1 and 5 and those claims dependent thereon. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 5, 7, 8, and 15 under 35 U.S.C. §102(b).

Conclusion

The present invention is not taught or suggested by the prior art. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims. An early Notice of Allowance is earnestly solicited.

Enclosed herewith, in duplicate, is a Petition for extension of time to respond to the Examiner's Action. Form PTO 2038 Credit Card Payment to cover the extension fee is enclosed. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 19-5425.

Respectfully submitted,

June 10, 2005
Date

Jonathan M. Dermott, Ph.D.
Registration No. 48,608

SYNNESTVEDT & LECHNER LLP
2600 ARAMARK Tower
1101 Market Street
Philadelphia, PA 19107

Telephone: (215) 923-4466
Facsimile: (215) 923-2189